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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 14

Application Number	10/762,652
Filing Date	22 Jan 04
First Named Inventor	Pravin PATE
Group Art Unit	1626
Examiner Name	San-Ming HUI, Esq.
Attorney Docket Number	Triax

ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
- ☒ Affidavits/declaration(s) R. Hamer
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) *(please identify below)*:

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Mark Pohl, Esq., USPTO Reg. No. 35,325 Pharmaceutical Patent Attorneys, LLC 55 Madison Avenue, 4th floor, Morristown, NJ 07960-7397 USA
Signature	/s/
Date	see below date

CERTIFICATE OF MAILING

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J. Mark Pohl, Reg. No. 35,325
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The submitted papers are enumerated on the enclosed Transmittal Form, PTO Form SB/21.

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In The United States Patent Office

In re Application of Pravin M. PATEL, *Stabilized Steroid Composition And Method for Its Preparation*

Serial No.: 10/762,652
Filing Date: 22 January 2004

DECLARATION UNDER 37 C.F.R. § 1.132

I Richard Hamer hereby make this Declaration under 37 Code of Federal Regulations § 1.132.

1) I respectfully believe that my academic training and professional experience qualify me as one of skill in the art of Food & Drug Administration regulatory affairs. I attach a copy of my *curriculum vitae* summarizing my academic training and professional experience.

2) I have read and understand the prior art of record, including Mark W. GRINSTAFF *et al., Methods for In Vivo Delivery...*, United States Letters Patent No. 5,560,156 combined with John E. HOOVER *et al., Remington's Pharmaceutical Sciences* pp. 956-71 (18th ed., 1990).

3) Hydrocortisone 17-butyrate is a topical steroidal anti-inflammatory agent. It is used topically. It is commercially available in The United States as a

topical cream, a topical lotion, a topical ointment, and a topical solution. This is evidenced by the United States Food & Drug Administration's *Therapeutic Drug Equivalents* (Orange Book) listing for the drug product hydrocortisone 17-butyrate. (copy attached) These Food & Drug Administration records show that hydrocortisone 17-butyrate is only available as a topical drug product.

4) Hydrocortisone 17-butyrate is not currently available in the United States in any non-topical formulation. To the contrary, on information and belief formed after a reasonable inquiry, no non-topical drug product containing hydrocortisone 17-butyrate has been approved as safe and effective by The Federal Food & Drug Administration. The sale of such a non-approved drug product would constitute the sale of an unapproved new drug product. This would violate The Federal Food, Drug & Cosmetics Act, 21 U.S.C.

5) Grinstaff *at e.g.*, 26:21-31; 26:45-51, enumerates many drugs potentially suitable for inclusion in the interior fill of his synthetic blood micro spheres. Grinstaff, however, fails to mention hydrocortisone 17-butyrate. This is not surprising because Grinstaff teaches an intravenous blood substitute, while hydrocortisone 17-butyrate is not recognized in the art as being acceptable for intravenous administration. Thus, an artisan of skill

in the art to which Grinstaff pertains would not consider hydrocortisone 17-butyrate suitable for inclusion in Grinstaff's micro spheres.

6) Grinstaff at 26:6-31 teaches to fill his micro spheres with cytotoxic drugs, nonsteroidal anti-inflammatory agents, steroids, and / or immunosuppressive agents.

7) Grinstaff teaches to dissolve these agents in a fluorocarbon, soybean oil, safflower oil, coconut oil, olive oil, cotton seed oil or other biocompatible oil.

8) Grinstaff, however, fails to teach that the fluorocarbon or bio-compatible oil must contain omega-6 acid. to the contrary, Grinstaff teaches to use several oils (*e.g.*, fluorocarbons, coconut oil) which do not contain omega-6 acid.

9) Grinstaff also fails to mention that the fluorocarbon or bio-compatible oil must contain omega-6 acid in an amount sufficient to stabilize hydrocortisone 17-butyrate.

10) Hydrocortisone is not interchangeable with hydrocortisone 17-butyrate, which is more potent corticoteroid. For example, hydrocortisone 17-butyrate is approved only for topical administration. In contrast, hydrocortisone is approved for systemic administration as an intramuscular injection, as an enema and as an oral dosage. *See* Hoover

at 965. The art of record cautions that while hydrocortisone may also be administered topically, "Systemic side effects can result from topical application." *Id.*

11) Similarly, hydrocortisone 17-butyrate degrades to hydrocortisone 21-butyrate. No evidence shows that hydrocortisone degrades into hydrocortisone 21-butyrate. Hydrocortisone lacks a butyrate moiety. Hydrocortisone would therefore not be expected to degrade into hydrocortisone 21-butyrate, nor into any other butyrate form.

12) This may be quite advantageous when administering a medical imaging agent. This would, however, render a topical medicine like hydrocortisone 17-butyrate inoperable. Adding hydrocortisone 17-butyrate to Grinstaff's micro spheres would sequester the hydrocortisone 17-butyrate, rendering it unavailable and ineffective.

13) Further, Grinstaff teaches that the micro spheres would sequester the hydrocortisone 17-butyrate for at least a month. Hydrocortisone 17-butyrate, however, is administered as a *skin cream*; thus, if the patient bathes at least once a month (a likely assumption for a patient who has access to prescription drugs such as hydrocortisone 17-butyrate) the patient would wash away the intact micro spheres - and their drug load - before the drug is released.

14) A patient could conceivably open the micro spheres by washing the micro sphere-treated skin with an organic solvent such as mercaptoethanol. This would be counter-productive, however, because organic solvent dries and damages skin. Compounding the problem, hydrocortisone 17-butyrate is used to treat eczema - already sensitive skin - so washing eczema-affected skin with an organic solvent would *exacerbate* the eczema, not ameliorate it.

15) In contrast to what the prior art teaches, I have found a way to stabilize hydrocortisone 17-butyrate. The instant Specification shows that after 6 months of storage at 40° C, an eczema skin cream made without added omega-6 acid has **9.17%** total impurities (6.36 % hydrocortisone 21-butyrate and 2.81% other impurities). In contrast, the same skin cream with added omega-6 acid has only **5.56%** total impurities (5.00 % hydrocortisone 21-butyrate and 0.56% other impurities).

16) I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title

18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

Signature :
Name : RICHARD A. HAMER
Dated as of : November 27, 2007

Attachments

Curriculum vitae.

The United States Food & Drug Administration's *Therapeutic Drug Equivalents* (Orange Book) listing for the drug product hydrocortisone 17-butyrate.

SD:\Tylex Pharma\10.762,652 R 132 Declaration - Hamer (Dec. 2007).doc

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Richard A. Hamer, RAC

Experience

2001-2003 Ferndale Laboratories, Inc. Ferndale, MI

Vice President, Regulatory/Clinical Affairs and QA

Responsible for staffing, training, managing and motivating regulatory affairs (4), clinical (3) and quality assurance (15) staff. Provide consultative (advisory) services as relates to implications of new product ideas, marketing approaches, and proposed manufacturing or analytical changes. Develop and implement regulatory strategies to secure approval of new and improved products in shortest possible time frame. Provide accurate interpretations and projections of future regulatory developments that may or will have a significant impact on FLI products. Establish and maintain effective working relationships with the FDA and international regulatory agencies.

1983 -2001 Richard Hamer Associates, Inc. Fort Worth, TX

Regulatory Consultant

Provide a full range of regulatory affairs consulting services to pharmaceutical and medical device manufacturers, including:

- Regulatory strategic planning.
- Preparation of investigational and marketing approval applications for new drug products and medical devices (IND, NDA, ANDA, IDE, PMA, 510(k), etc.).
- Drug Master File preparation.
- Clinical study monitoring.
- Compliance reviews of labeling and advertising.
- cGMP and QSR audits.
- FDA liaison and troubleshooting.

1982 - 1983 Alcon Laboratories, Inc. Fort Worth, TX

Consultant

Coordinated company defense efforts in U.S. vs. Alcon Laboratories (Puerto Rico), Inc. ("new drug" status law suit).

1981 - 1982 Alcon Laboratories, Inc. Fort Worth, TX

Acting Head, Regulatory Affairs

In addition to operational duties (see below), managed corporate regulatory affairs department. Coordinated with Corporate R&D, Manufacturing and Quality Assurance on regulatory issues.

1979 - 1982 Alcon Laboratories, Inc. Fort Worth, TX

Director, Regulatory Affairs - Dermatology

Managed all regulatory functions for Dermatology (Owen Laboratories) and Beauty Care (Allercreme/DuBarry/Mahdeen) Divisions, including:

- Advising Division management regarding regulatory strategies for new or improved products, proposed manufacturing or analytical changes, acquisitions and licensing agreements.
- FDA liaison.
- Review, submission, and approval monitoring of investigational and marketing approval applications (IND, NDA, ANDA).
- Review and approval of labeling, advertising and promotional materials
- Corporate cGMP compliance audits.

1974 - 1979 Alcon Laboratories, Inc. Fort Worth, TX

Manager, Regulatory Compliance

Managed all regulatory functions for Webcon (Pediatrics/Urology products) (1974-79) and Avicon (Surgical products) (1976-79) Divisions, including:

- Advising Division management regarding regulatory strategies for new or improved products, proposed manufacturing and analytical changes, acquisitions, and regulatory implications of marketing strategies.
- FDA liaison.
- Review, submission and approval monitoring of investigational and marketing approval applications (IND, NDA, ANDA and PMA)
- Review and approval of labeling, advertising and promotional materials.
- Corporate cGMP audits.

1973 - 1974 E.R. Squibb & Sons, Inc. Princeton, NJ

Clinical Coordinator - International Regulatory Affairs

- Evaluated clinical data for use in worldwide product registration programs.
- Prepared clinical data summaries for presentation to regulatory authorities in approximately 80 foreign countries.
- Enumerated clinical trial requirements for worldwide registration of new products and relicensing of marketed products.
- Coordinated foreign clinical trials required exclusively for product registration.
- Liaison with local subsidiaries.

1969 - 1973 E.R. Squibb & Sons, Ltd. Montreal, Canada

Coordinator – Drug Regulatory Affairs

- Evaluated CMC, preclinical and clinical data for preparation of Canadian product registration submissions.
- Liaison with HPB Canada on registration issues.
- Liaison with Squibb International Regulatory Affairs staff and consulting laboratories.
- Reviewed and approved labeling and promotional materials.

Education

1984 University of Texas at Arlington Arlington, Texas

Master of Business Administration

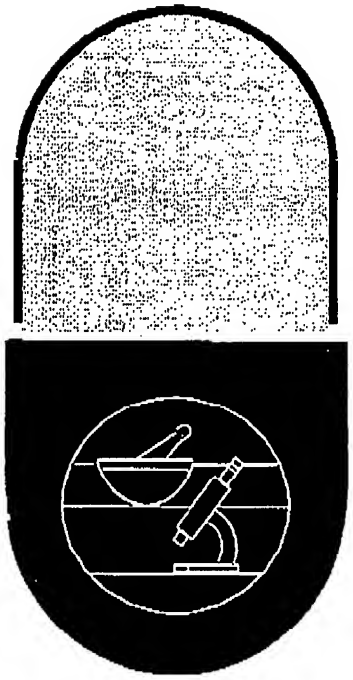
- Major in Economics and Marketing

1969 McGill University Montreal, Canada

Bachelor of Science

- Chemistry/Biochemistry

Professional Memberships	Regulatory Affairs Professionals Society (Regulatory Affairs Certified) Food and Drug Law Institute
Languages	Fluent in Dutch; good working knowledge of French; some German.
Computer Skills	MSWord, WordPerfect, Excel



APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

27th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2007

APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2006.

27th EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2007

PRESCRIPTION DRUG PRODUCT LIST 3 - 199 (of 370)

HYDROCORTISONE ACETATE						
	POWDER; FOR RX COMPOUNDING					
	HYDROCORTISONE ACETATE					
	X GEN PHARMS	100%		N85981	001	
HYDROCORTISONE ACETATE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE						
	CREAM; TOPICAL					
	CORTISPORIN					
	+ MONARCH PHARMS	0.5%;EQ 3.5MG BASE/GM;10,000 UNITS/GM		N50218	001	Aug 09, 1985
HYDROCORTISONE ACETATE; OXYTETRACYCLINE HYDROCHLORIDE						
	SUSPENSION/DROPS; OPHTHALMIC					
	+ PFIZER	1.5%;EQ 5MG BASE/ML		N61016	001	
HYDROCORTISONE ACETATE; PRAMOXINE HYDROCHLORIDE						
	AEROSOL, METERED; TOPICAL					
	EPIFOAM					
BX	SCHWARZ PHARMA	1%;1%		N86457	001	
	HYDROCORTISONE ACETATE 1% AND PRAMOXINE HYDROCHLORIDE 1%					
BX	BOCA PHARMA	1%;1%		N89440	001	May 17, 1988
	PROCTOFOAM HC					
BX	SCHWARZ PHARMA	1%;1%		N86195	001	
	CREAM; TOPICAL					
	PRAMOSONE					
	FERNDALE LABS	0.5%;1%		N83778	001	
		1%;1%		N85368	001	
	LOTION; TOPICAL					
	PRAMOSONE					
	FERNDALE LABS	1%;1%		N85980	001	
		2.5%;1%		N85979	001	
HYDROCORTISONE ACETATE; UREA						
	CREAM; TOPICAL					
	CARMOL HC					
AT	+ KENWOOD LABS	1%;10%		N80505	001	
	U-CORT					
AT	TARO	1%;10%		N89472	001	Jun 13, 1988
HYDROCORTISONE BUTYRATE						
	CREAM; TOPICAL					
	HYDROCORTISONE BUTYRATE					
AB	TARO PHARM INDS	0.1%		N76654	001	Aug 03, 2005
	LOCOID					
AB	+ FERNDALE LABS	0.1%		N18514	001	Mar 31, 1982
	LOCOID LIPOCREAM					
	+ FERNDALE LABS	0.1%		N20769	001	Sep 08, 1997
	OINTMENT; TOPICAL					
	HYDROCORTISONE BUTYRATE					
AB	TARO	0.1%		N76842	001	Dec 27, 2004
	LOCOID					
AB	+ FERNDALE LABS	0.1%		N18652	001	Oct 29, 1982
	SOLUTION; TOPICAL					
	HYDROCORTISONE BUTYRATE					
AT	TARO PHARM INDS	0.1%		N76364	001	Jan 14, 2004
	LOCOID					
AT	+ FERNDALE LABS	0.1%		N19116	001	Feb 25, 1987